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Investigation of chronic diarrhoea in infancy

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ABSTRACT

Diarrhoea in infants and young children is defined as >200 g/day of stools, and occurs when there is an imbalance between intestinal fluids absorption and secretion. This may be caused by either a decreased absorption (osmotic diarrhoea) or an increased secretion (secretory diarrhoea). Chronic diarrhoea defines intestinal loss of water and electrolytes with increased stool frequency, reduced consistency and larger volume over more than 14 days. This disorder in children shows a wide range of aetiologies depending on the age. The knowledge of common and rare aetiologies is important to optimize the diagnostic approach. A stepwise approach, starting with a comprehensive history, physical examination, inspection and collection of stool samples, helps to devise appropriate diagnostic and therapeutic management. In this article we discuss the pathophysiology, aetiology and possible approach to chronic diarrhoea in infancy.

Contents

1. Introduction

Chronic diarrhoea (CD), defined as the persistence of loose stools (generally with an increase in stool frequency) for at least 14 days [1], is a symptom complex with a variety of underlying aetiologies changing with age even within infancy and childhood. Moreover, the aetiologic spectrum of CD in infants includes congenital diarrhoeal disorders (CDDs) that occur typically within the first weeks of life and require a tertiary care centre for diagnosis and treatment [2]. The aim of this review is to focus on the major clinical aspects of diarrhoea in infancy suggesting a stepwise diagnostic approach in order to limit unnecessary invasive procedures thereby resulting in a better management of infants.

2. Mechanisms leading to chronic diarrhoea in infancy

Chronic diarrhoea may be divided into two main basic categories: secretory diarrhoea (SD) and osmotic diarrhoea (OD); however, in several cases, both mechanisms may be involved. Secretory diarrhoea is

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usually characterized by a large volume of watery stools, lasts even when oral food is interrupted and has increased electrolyte and water fluxes towards the intestinal lumen resulting from either the inhibition of NaCl absorption by villous enterocytes or the increase in chloride secretion by secretory crypt cells. The aetiology of SD may be of infectious (bacteria, viruses and protozoan agents) or of non-infectious nature (hormones, neurotransmitters, cytokines, etc.). Osmotic diarrhoea is caused by the presence of non-absorbed nutrients in the gastrointestinal tract and is usually associated with intestinal damage. Non-absorbed solutes drive water into the lumen through an osmotic force. An example of osmotic diarrhoea is lactose malabsorption associated to congenital or acquired lactose intolerance. The intestinal microflora ferments the sugar to short-chain organic acids, creating an osmotic load which drives water into the lumen. In general, OD occurs whenever digestion and/or absorption are impaired, because of reduction or absence of pancreatic enzymes and bile acid disorders. Intestinal absorption depends not only on intact epithelium, but also on adequate time for digestion and contact between the nutrients and the absorptive surface. Thus, alterations in intestinal transit times, particularly reductions in small intestinal and whole gut transit times, may lead to impaired nutrient, electrolyte and water intestinal absorption. Moreover, increased gut permeability, due to inflammation or cytotoxic agents, causes an excessive protein loss as in protein-losing enteropathies [3].

3. The aetiology of chronic diarrhoea in infancy

The aetiology of CD in infancy is mainly related to the age of onset, as depicted in Table 1. In neonatal period, diarrhoea is relatively rare, but its early onset may be predictive of congenital diarrhoeal disorders and requires hospitalization [4]. Several conditions, starting in neonatal age, are related to genetic defects. Apart from congenital disorders, CD is largely dependent on socio-economic factors and on clinical situation. Intestinal infections are the main cause of CD in developing countries, where they, usually, have a protracted and complicated course being the majority of children affected by malnutrition. In developed countries, the spectrum of aetiology of CD includes functional disorders, nutrient malabsorption (such as food allergy, celiac disease, and cystic fibrosis), autoimmune enteropathy, and persistent infections of the intestinal tract.

Table 1
Main causes of chronic diarrhoea in infancy according to the age of onset.

0–30 days	1–12 months
Abetalipoproteinemia	Apple juice and pear nectar
Acrodermatitis enteropathica	Autoimmune enteropathy
Autoimmune enteropathy	Chronic infection by *C. difficile*, *G. lamblia*
Congenital chloride diarrhoea	Chronic non-specific diarrhoea
Congenital sodium diarrhoea	Celiac disease
Congenital short-bowel syndrome	Cystic fibrosis
Congenital lactase deficiency	Food allergy
Disaccharide intolerance	Post-gastroenteritis diarrhoea
Food allergy	
Glucose–galactose malabsorption	
Hirschsprung's disease	
Immunodysregulation, polyendocrinopathy and enteropathy (IPEX)	
Lysinuric protein intolerance	
Malrotation with partial blockage	
Microvillous inclusion disease	
Neonatal lymphangiectasia	
Primary bile–salt malabsorption	
Tufting enteropathy	
Intestinal pseudo-obstruction	

4. Congenital diarrhoeal disorders

Congenital diarrhoeal disorders are a group of inherited enteropathies with a typical onset early in life [5]. Most CDDs display similar clinical presentation despite different outcomes. For many of these conditions, severe chronic diarrhoea represents the main clinical manifestation, while in others, diarrhoea is only a component of a more complex multi-organ or systemic disease. In the vast majority of cases appropriate therapy must be started immediately to prevent dehydration and long-term, and sometimes life-threatening, complications. Milder forms of CDDs, with less severe clinical picture that remains undiagnosed until later ages, have been described. The less severe outcome may depend on a milder effect of mutations in the disease gene. In most cases of CDDs the disease-gene is known [6]. Thus, molecular analysis has become a major advantage in the difficult diagnostic approach to a patient with suspected CDDs.

We proposed a CDD classification in four groups [5]:

(i) Defects of digestion, absorption and transport of nutrients and electrolytes;
(ii) Defects of enterocyte differentiation and polarization;
(iii) Defects of enteroendocrine cell differentiation;
(iv) Defects of modulation of intestinal immune response.

This classification could be adopted as a practical starting point for the complex diagnostic approach to patients with CDDs. The diagnostic approach to CDDs is a multistep process that includes the careful evaluation of the anamnesis and clinical data, results of common laboratory and instrumental procedures and molecular analysis. Positive familiar history of early onset chronic diarrhoea, polyhydramnios and/or dilated bowel loops at ultrasound examination during pregnancy are highly suggestive of CDDs. Frequently CDDs date to early neonatal period [6]. However in the approach to a newborn or infant with suspected CDDs it is important to remember that also at this particular age, infections and food allergy are frequent causes of chronic diarrhoea, and that these conditions together with malformations of gastrointestinal tract should be considered as primary hypothesis.

Once suspected, the fundamental step in the diagnostic process of CDDs is the identification of an osmotic or secretory mechanism leading to diarrhoea. Furthermore, the determination of stool electrolyte concentration and faecal ion gap is important to discriminate the two mechanisms responsible for CDDs. If the ion gap is >50, faecal osmolarity is derived from ingested osmotically active nutrient or nonmeasured ion (i.e., Cl^-, Mg^{2+}). In contrast a low osmotic gap (<50) is typically observed in secretory diarrhoea. It is also important to measure Cl^- concentration in the stool to rule out congenital chloride diarrhoea (CCD), which is characterized by low ion gap due to high Cl^- faecal loss (>90 mmol/L) [3]. When an osmotic mechanism is suspected, the next step of laboratory investigation includes determination of blood gas, blood glucose, ammonium, albumin, triglycerides and cholesterol, and aminoaciduria and the search for reducing substances in the stools, steatocrit and sweat test. Finally, intestinal biopsy with hystologic examination is crucial for the diagnosis of most CDDs, more frequently for secretory forms; even if molecular analysis, when available, could limit invasive procedures.

In the majority of cases genes responsible for CDDs are not particularly large. This permits using scanning techniques like the gene sequencing for molecular analysis, in order to reduce diagnostic errors. Furthermore, some CDDs in specific ethnic groups are caused by a single mutation due to the founder effect, while the same diseases in other ethnic groups may be due to a myriad of different mutations. In some CDDs (like glucose–galactose malabsorption, immune dysfunction-polyendocrinopathy-X-linked syndrome, cystic fibrosis) [6], molecular analysis has been used for prenatal diagnosis. Given the severe outcome of most CDDs, and the availability of efficient techniques for gene scanning analysis, the request for prenatal diagnosis will increase in the

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future. It is important that prenatal diagnosis would be associated to a careful multidisciplinary counselling to the families.

5. Infectious aetiologies

Intestinal infections are always a potential aetiology of chronic diarrhoea and single agents show a peculiar distribution. Entero-adherent *Escherichia coli* and *Cryptosporidium parvum* have been implicated in potentially severe chronic diarrhoea in developing countries. In developed countries chronic infectious diarrhoea usually runs a benign course and the aetiology is often viral. *Rotavirus* and *Norovirus* are frequently involved, whereas *Cytomegalovirus* and *Clostridium difficile* are emerging agents of severe diarrhoea in selected populations. Opportunistic microorganisms induce diarrhoea exclusively or more severely or longer than expected, in specific populations, such as immunocompromised children. Post-enteritis syndrome is a clinical–pathological condition in which small intestinal mucosal damage persists following acute gastroenteritis. Sensitization to food antigens and secondary disaccharidase deficiency were considered as responsible for post-enteritis syndrome. Another mechanism of post-enteritis syndrome is believed to be an infection or re-infection with an enteric pathogen. Small bowel bacterial overgrowth induces chronic diarrhoea through multiple mechanisms: an increase of over 10^5 CFU/ml in duodenal fluid, or the presence of anaerobic bacteria species is considered to be responsible for severe impairment of digestive and absorptive processes [1,3].

6. Non-infectious aetiologies

A reduction of intestinal absorptive surface is responsible for diarrhoea in celiac disease. Gliadin induces villous atrophy leading to a reduction of the functional absorptive surface area that is reversible upon implementation of a strict gluten free diet. Food allergies may present with chronic diarrhoea through a non-IgE-mediated mechanism, especially during infancy [5]. Eosinophilic gastroenteritis is characterized by eosinophilic infiltration of the intestinal wall and is strongly associated with atopy. Disorders of intestinal motility are a group of intestinal diseases associated with chronic diarrhoea. Motility disorders include alterations of the enteric nervous system development and function, such as in Hirschsprung's disease, aganglionosis and chronic intestinal pseudoobstruction [7]. Other motility disorders may be secondary to extra-intestinal disorders, such as in hyperthyroidism. Short gut syndrome is associated with chronic diarrhoea. All intestinal abnormalities such as stenosis, segmental atresia, and malrotation may require surgical resection. In these conditions, the residual intestine may be insufficient in its normal digestive–absorptive functions.

7. Approach to the infant with chronic diarrhoea

The main aetiologies of chronic diarrhoea should be investigated, based on the features of diarrhoea, and their predominant or selective intestinal dysfunction. A step by step diagnostic approach is important to minimize the invasiveness to the child, and the overall costs, while optimizing the yield of the diagnostic work-up (Fig. 1). Because of the wide aetiologic spectrum of chronic diarrhoea in children, the plan of investigations should start from 3 main information: age of the child, weight pattern and the malabsorption or – conversely – inflammation pattern of stools and associated symptoms. As a consequence, endoscopy should rarely be the first step, and efforts should be made to limit it. However, a careful history and physical examination are the cornerstones of a diagnostic approach. Key data from the history include the age of onset of diarrhoea, and whether this was abrupt or gradual at its onset. Age needs to be considered together with stool characteristics (secretory, osmotic, or mixed) and the presence or absence of malabsorption in order to plan a diagnostic algorithm based on the best probability to find the primary cause of chronic diarrhoea. A family history is always crucial in assessing the possibility of inherited conditions or disease. History of chronic/intractable diarrhoea in a relative suggests a genetic disease, particularly if presentation occurred in the first months of life. A family history positive for autoimmune or atopic diseases points towards allergy or autoimmunity. The same is often true for children with cystic fibrosis. Many CDD conditions (i.e., microvillous inclusion disease) are associated with consanguinity. However, a negative family history does not rule out the possibility that the infant or child has an inherited disease. The presence of polyhydramnios is consistent with congenital chloride or sodium diarrhoea. A previous episode of acute gastroenteritis is suggestive of post-enteritis syndrome, whereas the association of diarrhoea with ingestion of specific foods should always be looked for possible intolerance to one or more food antigens. Initial clinical examination should include the evaluation of general and nutritional status. It is not rare to face critical clinical condition with dehydration,

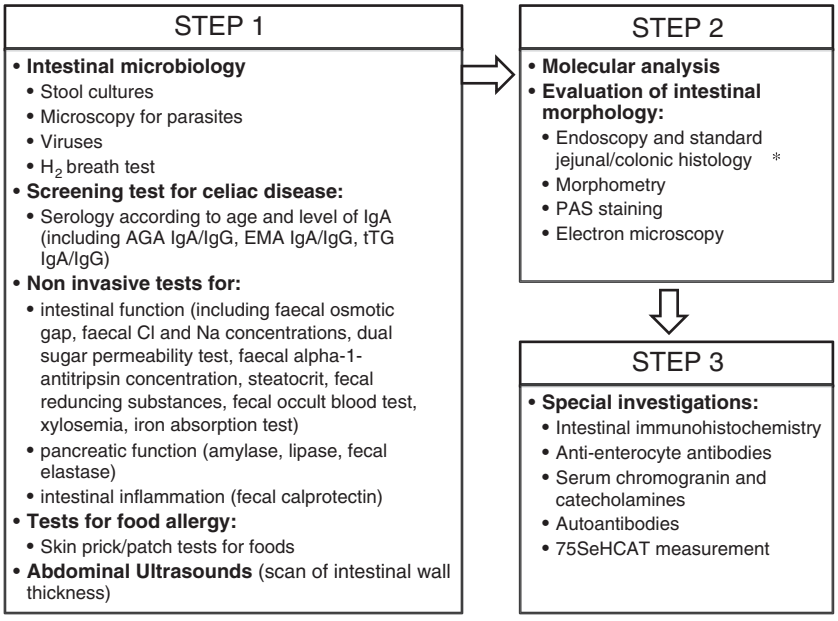

Fig. 1. Multistep diagnostic work-up for chronic diarrhoea in infancy.

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marasmus or kwashiorkor, requiring prompt supportive interventions to stabilize the patient. The presence of eczema or asthma is associated with an allergic disorder, and specific extra-intestinal manifestations (arthritis, diabetes, thrombocytopenia, etc.) may suggest an autoimmune disease. Specific skin lesions may be suggestive of enteropathic acrodermatitis. Typical facial abnormalities, and wholly hair are associated with phenotypic diarrhoea.

Another most important issue in the initial approach is growth and nutritional assessment. Although there are many ways to perform a nutritional assessment, such as the dosage of biochemical markers including albumin, prealbumin, retinol binding protein, transferrin, serum iron, iron binding capacity, and micronutrient concentrations, or the assessment of body composition, and weight for height is the simplest index of growth failure secondary to malnutrition. Sequential heights and weights, with measurement of head circumference, are critical for determining whether the disease has impaired growth. Height is generally involved later than weight in chronic diarrhoea and its impairment suggests a long standing condition. Poor weight gain may be due to malabsorption and deficit energy intake, or be secondary to changes in metabolism, as in hyperthyroidism. Poor growth may be due to feeding a dilute hypocaloric formula or clear liquids in an effort to reduce diarrhoea.

Examination of the stool is an integral part of the investigation. Visual inspection of the stool will give important information. Stool features (watery, presence of blood and mucus, presence or absence of undigested food particles, steatorrhoea) may aid in establishing the pathophysiology of diarrhoea, that could be secretory, inflammatory, osmotic, malabsorptive, or functional in nature. Microbiological stool cultures will indentify the agents responsible for diarrhoea. Stool frequency and volume may aid in establishing the diarrhoea severity. Indicators of a functional aetiology are a long duration of symptoms, the lack of significant weight loss, and absence of nocturnal diarrhoea. In children with normal weight growth, the most probable cause is functional diarrhoea. Functional diarrhoea only requires monitoring, whereas parents need to be reassured on the benign outcome of the condition. The Rome III diagnostic criteria are helpful to obtain a final diagnosis in these cases (Table 2). Abdominal distension could be secondary to true obstruction, pseudo-obstruction, malabsorption, or hypersecretion of liquids in the intestine. The presence of fever is more typical of infectious or inflammatory processes. Recurrent respiratory tract infections could suggest cystic fibrosis, or immunodeficiency.

In infants with chronic diarrhoea, feeding history must be carefully obtained. If an infant is or was formula-fed when the diarrhoea began, the type of formula and the response to it should be considered and a careful history of the mother's diet must be determined. Any change of formula and the respective clinical response should be accurately recorded. Onset of diarrhoea soon after fruit and juice are added is typical of sucrase–isomaltase deficiency. On the contrary, typical symptoms of celiac disease may not develop for weeks, months, or even years after gluten is added to the diet. However if weight is impaired, in all cases of persistent diarrhoea, irrespective of risk factors, the diagnostic work-up should start from non-invasive tests to investigate the digestive–absorptive functions and the presence of inflammation. These are quite standardized investigations, although not widely available, and provide reliable information on the intestinal segment and functions involved as well as the presence of inflammation. Moreover, electrolyte concentrations in faecal samples discriminate between secretory and osmotic diarrhoea and may provide important information for guiding the subsequent diagnostic approach (Table 3), and the differentiation between a pattern of inflammation, rather than malabsorption, or a pattern consistent with functional disorders is essential in planning the diagnostic work-up. If stools do not contain occult or gross blood, granulocytes, and eosinophils, an inflammatory or food allergy could be reasonably excluded.

Table 2
Rome III criteria for functional diarrhoea in neonate and toddlers.

- Daily painless, recurrent passage of 3 or more large, unformed stools
- Symptoms that last more than 4 weeks
- Onset of symptoms that begin between 6 and 36 months of age
- Passage of stools that occurs during waking hours
- There is no failure-to-thrive if caloric intake is adequate

Table 3
Stool features supporting the differential diagnosis between secretive and osmotic diarrhoea.

	Secretory	Osmotic
Osmotic gap	<50 mOsm/kg	>135 mOsm/kg
Cl^- concentration	>40 mEq/L	<35 mEq/L
Na^+ concentration	>70 mEq/L	<70 mEq/L

Large volumes of loose stools or steatorrhoea indicate nutrient malabsorption. Celiac disease is likely the single most frequent cause of chronic diarrhoea and serology is a needed test in children of any age on gluten containing diet, as indicated by the updated guidelines [8].

Microbiological investigation of stool samples should include a thorough list of agents, and may provide valuable information. Search for proximal intestinal bacterial overgrowth is part of a microbiological investigation. The breath hydrogen test, after glucose oral load, may identify an abnormal bacterial proliferation in the small bowel. Breath test can also be used for detecting carbohydrate malabsorption. Moreover, calprotectin, a protein highly present in neutrophils, is commonly used to detect gut inflammation [9]. It may be a screening test alone or in combination with other non-invasive tests, before an endoscopy, especially in children with suspected IBD [10].

Generally abnormalities in nutrient absorption tests may indicate a proximal bowel endoscopy whereas increased inflammation suggests to proceed with recto-sigmoidoscopy or colonoscopy. Their use in association with a stepwise approach strongly reduced the need for invasive investigations and associated costs [1]. Colonoscopy should be performed in all cases of chronic diarrhoea in which gross or occult blood is detected in the stools, or when an increased frequency of mucous stools and abdominal pain suggests colonic involvement. Biopsies should be performed at multiple sites, even in a normally appearing intestine, because at least 5% of apparently normal colons will yield specimens positive for colitis, when a disease characterized by patchy lesions is responsible for the observed symptoms. Histology is important to establish the degree of mucosal involvement, through grading of intestinal damage and the presence of associated abnormalities, such as inflammatory infiltration of the lamina propria. Morphometry provides additional quantitative information of epithelial changes. It should be pointed out however that in a number of cases, endoscopy does not provide a conclusive diagnosis. Imaging has some place in the diagnostic approach to children with chronic diarrhoea, but is less important than in adults. Abdominal ultrasound may help in detecting a thickened distal bowel wall pointing to Crohn's diseases, and abdominal X-ray is useful for detection of gaseous distension, suggestive of a gastrointestinal obstruction. Structural abnormalities such as diverticula, malrotation, stenosis, blind loop, as well as motility disorders, may be appreciated after a barium meal and an entire bowel follow-through examination.

8. Conclusions

Chronic diarrhoea is still a major problem worldwide, but with two distinct presentations. In developing and transitional countries, chronic diarrhoea is a relatively frequent outcome of intestinal infections and is loaded with high case/fatality ratio, mainly because of the combined effect of enteric infections, intestinal dysfunction, malnutrition and immune suppression. In industrialised countries chronic diarrhoea usually has a benign course with viral infections playing a major role. However, the aetiologic spectrum may be broader with an increase of early-onset severe cases, generally evolving towards irreversible intestinal diseases. In these cases, optimal diagnostic approach and general

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management require advanced knowledge and technology, and should be carried on in tertiary care centres or through a close interaction among experts in gastroenterology, nutrition, infectious diseases and paediatric surgery.

Conflict of interest statement

The authors reported no potential conflicts of interest relevant to this article.

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